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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,327	08/08/2001	Patricia D. Murphy	044921-5054-02	3339

9629 7590 04/21/2004

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EXAMINER

MYERS, CARLA J

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/923,327

Applicant(s)

MURPHY, PATRICIA D.

Examiner

Carla Myers

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 January 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 97-101, 103 and 105-124 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. This action is in response to the amendment filed January 15, 2004. Applicants amendments and arguments have been fully considered. In view of the amendments to the claims, the previous grounds of rejection are withdrawn. However, this action contains new grounds of rejection necessitated by Applicants amendments to the claims. This action is made final.

Election/Restrictions

2. Applicant's election with traverse of Group I in the response of January 15, 2004 is acknowledged. The traversal is on the ground(s) that each of the sequences set forth in Table 9 should be examined with the elected invention. Applicants argue that the "Examiner must give an example of an alternative use for any one of the oligonucleotides recited in these claims (see MPEP 806.04(b) in order to establish that they are distinct." Applicant's arguments are not found persuasive because there is no requirement to show that the oligonucleotides may be used in alternative manners. MPEP 806.04(b) discusses restriction between **related** inventions and provides an example in which an intermediate and final product may be appropriately restricted if alternative uses for the products can be demonstrated. However, the claims that were restricted in the previous Office action are NOT drawn to related inventions or to inventions related as intermediate and final products. The oligonucleotides set forth in Table 9 are drawn to structurally distinct molecules. The methods using these sequences constitute independent and distinct inventions and were subject to a

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restriction requirement and not to an election of species requirement. The requirement is still deemed proper and is therefore made FINAL.

Further, claims 122-124 have been rejoined with group I in view of the amendment to these claims.

Priority

3. It is noted that the priority information set forth on the first page of the specification is unclear. This priority statement indicates that application 08/598,591, filed February 12, 1996, is a continuation-in-part of 09/084,471, filed March 22, 1998. However, since the '591 application was filed before the '471 application, the '591 application cannot be a continuation-in-part of the '471 application.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY
APPLICANTS AMENDMENTS TO THE CLAIMS:

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 97-101, 103, and 105-124 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining that an individual has the omi¹, omi² or omi³ BRCA1 haplotype, wherein the methods comprise determining the nucleotide or putative amino acid sequence of the BRCA1 gene of a human subject, comparing said sequence to the sequence of SEQ ID NO: 263 or 264, respectively, and optionally further comparing the determined sequence to

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the nucleotide sequence of SEQ ID NO: 265 or 267 or the amino acid sequence of SEQ ID NO: 266 or 268 and determining that the individual has the omi¹ BRCA1 haplotype if the individual has a T at position 2201, a C at position 2430, a T at position 2731, a G at position 3232, a G at position 3667, a C at position 4427 and a G at position 4956 (with respect to the numbering of SEQ ID NO: 263); determining that the individual has the omi² BRCA1 haplotype if the individual has a C at position 2201, a T at position 2430, a T at position 2731, an A at position 3232, an A at position 3667, a T at position 4427 and an A at position 4956 (with respect to the numbering of SEQ ID NO: 263); and determining that the individual has the omi³ BRCA1 haplotype if the individual has a T at position 2201, a C at position 2430, a T at position 2731, a G at position 3232, a G at position 3667, a T at position 4427 and a G at position 4956 (with respect to the numbering of SEQ ID NO: 263), does not reasonably provide enablement for methods for determining any haplotype of a human BRCA1 gene by determining the nucleotide sequence of the BRCA1 gene or a fragment thereof from a female individual whose family history indicates a predisposition to breast cancer, and comparing this sequence to SEQ ID NO: 263 wherein the presence of at least one variation in the determined nucleotide sequence indicates the haplotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the

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predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for determining a haplotype of a human BRCA1 gene by determining the nucleotide sequence of the BRCA1 gene or a fragment thereof from a female individual whose family history indicates a predisposition to breast cancer, and comparing the determined sequence to SEQ ID NO: 263, wherein the presence of at least one variation in the determined nucleotide sequence indicates the haplotype. The specification (page 2) notes that frequently there is not one single wild-type and one single mutant form of a gene. But rather there may be alternate wild-type and mutant forms of a gene that are defined by multiple variations throughout the gene. With respect to the BRCA1 gene, the specification teaches 3 haplotypes that are characteristic of "normal" BRCA1 genes. In particular, the BRCA1 haplotypes are omi^1 , omi^2 and omi^3 . The haplotypes are defined in terms of the nucleotides present at positions 2201, 2430, 2731, 3232, 3667, 4427 and 4965 of the BRCA1 gene (see Table 7 and Figure 1). Accordingly, the specification teaches how to determine whether an individual has the omi^1 , omi^2 or omi^3 BRCA1 haplotype by sequencing the BRCA1 gene of an individual and determining that the individual has the omi^1 BRCA1 haplotype if the individual has a T at position 2201, a C at position 2430, a T at position 2731, a G at position 3232, a G at position 3667, a C at position 4427 and a G at position 4956 (with respect to the numbering of SEQ ID NO: 263); determining that the individual has the omi^2 BRCA1 haplotype if the individual has a C at position 2201, a T at position 2430, a

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T at position 2731, an A at position 3232, an A at position 3667, a T at position 4427 and an A at position 4956 (with respect to the numbering of SEQ ID NO: 263); or determining that the individual has the omi³ BRCA1 haplotype if the individual has a T at position 2201, a C at position 2430, a T at position 2731, a G at position 3232, a G at position 3667, a T at position 4427 and a G at position 4956 (with respect to the numbering of SEQ ID NO: 263).

However, the specification does not teach how to determine any additional haplotypes by comparing the BRCA1 gene or fragment thereof of an individual to the sequence of SEQ ID NO: 263 because the specification has not adequately defined any additional BRCA1 haplotypes. As discussed in the specification at page 1, there are at least 125 mutations present in the BRCA1 gene. While the prior art teaches mutations in the BRCA1 gene, the present specification has not characterized additional haplotypes based on the presence of these mutations or on the presence of other mutations or polymorphisms in the BRCA1 gene. Additionally, the specification has not taught one of skill in the art how to determine the haplotypes of a BRCA1 gene based on the presence of a single nucleotide variation in any fragment of the BRCA1 gene. Haplotypes are composed of two or more variant positions. The specification does not teach any particular haplotypes which can be definitively identified by detecting a single variation in the BRCA1 gene. Further, several of the nucleotide polymorphisms that constitute the omi¹, omi² or omi³ BRCA1 haplotype do not result in an amino acid alteration (i.e., the nucleotide variations at positions 2201, 2430, 3232 and 4427 do not lead to a change in the amino acid sequence). Thereby, the specification has not taught

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how one can determine the haplotypes of an individual by comparing the putative amino acid sequence encoded by an individual's BRCA1 gene to SEQ ID NO: 264 at amino acid positions 694, 771, 1038 or 1436 and determining a haplotype based on the presence of a variation at this position. The specification has also not defined any alterations in intron sequences or taught how to determine an individual's haplotype based on the presence of specific variations in an individual's intron sequences as compared to SEQ ID NO: 263. Additionally, the specification does not provide sufficient guidance as to how to determine the haplotype of an individual by determining the nucleotide sequence of a fragment outside of nucleotide positions 2201, 2430, 2731, 3232, 3667, 4427 and 4956. While one could sequence the BRCA1 gene of a representative number of individuals that have breast cancer or do not have breast cancer or who have an increased susceptibility to breast cancer or have a low susceptibility to breast cancer (based on family histories), and could compare these sequences to one another and to the sequences of SEQ ID NO: 263, and could then analyze this information to try to identify additional haplotypes of the BRCA1 gene, such experimentation constitutes a research project and is considered to be undue. It is highly unpredictable as to which groupings of polymorphisms and/or mutations in the BRCA1 gene would together comprise a distinct haplotype. Further, insufficient guidance has been provided in the specification as to how to identify additional, specific haplotypes without undue experimentation. Providing methods of searching for additional BRCA1 haplotypes is not equivalent to providing specific BRCA1 haplotypes.

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For these reasons, the specification has not enabled one of skill in the art to practice the present haplotyping methods as they are broadly claimed.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 97-101, 103, and 105-124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 97-101, 103, and 105-124 are indefinite and vague. The claims are drawn to a method of determining the haplotypes of a human BRCA1 gene and recite steps of determining the nucleotide sequence of an individual's BRCA1 gene and comparing the determined nucleotide sequence to the sequence of SEQ ID NO: 263. The claims state that "the presence of at least one variation in the determined nucleotide sequence indicates the haplotypes." However, it is unclear as to how the presence of a variation indicates a haplotype. The claims do not set forth how a haplotype is determined, what constitutes the haplotype or how detecting a single variation at any position in the BRCA1 gene as compared to SEQ ID NO: 263 results in the determination of a haplotype.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

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1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 97-101, 103, and 105-124 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-7 of U. S. Patent No. 5,750,400. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '400 each include methods which require performing the steps of determining the sequence of the BRCA1 gene of an individual, comparing the determined sequence to the sequence of SEQ ID NO: 263 (referred to in '400 as SEQ ID NO: 1; omi¹) and determining the presence of a polymorphic variation in the individual's BRCA1 coding sequence. The claims of '400 also include comparing the sequence to the omi² and omi³ genes. While the claims of '400 are drawn to methods for identifying an individual's BRCA1 gene and do not specifically recite determining a haplotype, the claims of '400 effectively determine an individual's haplotype by detecting the variations in the BRCA1 gene set forth in claims 2-7 of '400. Further, the present claims recite that the presence of the variation is indicative of the haplotypes and the present claims do not recite any additional process steps which distinguish the method of haplotyping over the methods of '400. With respect to claims 107-110, 115-121, 123 and 124, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have

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alternatively, or in addition to the recited method steps, also analyzed the putative amino acid sequence encoded by the individual's BRCA1 gene and to have compared this sequence with the putative sequence encoded by SEQ ID NO: 263 in order to have identified the presence of amino acid variations. Furthermore, while the claims of '400 are limited to the analysis of an individual, the claimed methods are clearly applicable to larger populations. Thereby, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have repeated the methods of '400 so as to have analyzed the BRCA1 gene in additional individuals, thereby analyzing the BRCA1 gene in at least 50 or more individuals in order to have determined the presence of genetic variation in the BRCA1 gene of each of these individuals. Additionally, the ordinary artisan would have recognized the need to analyze individuals with a family history of breast cancer since these individuals would be most susceptible to developing breast cancer and could possibly be given early treatment intervention based on the analysis of their BRCA1 gene.

7. Claims 97-101, 103, and 105-124 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-4 of U. S.

Patent No. 5,654,155. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '155 each include methods which require performing the steps of determining the sequence of the BRCA1 gene of an individual, comparing the determined sequence to the sequence of SEQ ID NO: 263 (referred to in '155 as SEQ ID NO: 1; omi¹) and determining the presence of a polymorphic variation in the individual's BRCA1 coding

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sequence. The claims of '155 also include comparing the sequence to the omi² and omi³ genes. While the claims of '155 are drawn to methods for identifying an individual's BRCA1 gene and do not specifically recite determining a haplotype, the claims of '155 effectively determine an individual's haplotype by detecting the variations in the BRCA1 gene set forth in claims 2-4 of '155. Further, the present claims recite that the presence of the variation is indicative of the haplotype and the present claims do not recite any additional process steps which distinguish the method of haplotyping over the methods of '155. With respect to claims 107-110, 115-121, 123 and 124, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have alternatively or in addition to the recited method also analyzed the putative amino acid sequence encoded by the individual's BRCA1 gene and to have compared this sequence with the putative sequence encoded by SEQ ID NO: 263 in order to have identified the presence of amino acid variations. Furthermore, while the claims of '155 are limited to the analysis of an individual, the claimed methods are clearly applicable to larger populations. Thereby, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have repeated the methods of '155 so as to have analyzed the BRCA1 gene in additional individuals, thereby analyzing the BRCA1 gene in at least 50 individuals in order to have determined the presence of genetic variation in the BRCA1 gene of each of these individuals.. Additionally, the ordinary artisan would have recognized the need to analyze individuals with a family history of breast cancer since these individuals would be most susceptible to developing breast cancer and

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could possibly be given early treatment intervention based on the analysis of their BRCA1 gene.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Carla Myers

April 19, 2004


CARLA J. MYERS
PRIMARY EXAMINER